Sequence Listing and the Abstract are provided with this paper. Applicants also submit herewith a computer readable form containing the identical information in the substitute Sequence Listing and a statement pursuant to 37 CFR §1.825(a) and (b).

The claims have been amended to address formal rejections imposed by the Examiner and to more clearly set forth what is regarded by Applicants as their invention. Support for the amendments to claim 4 appears in Table 2 (pages 25-29); support for the amendments to claims 6, 9 and 12 is seen on page 17, lines 17-23.

In the Office Action (paper no. 7), page 2/paragraph 1, the Examiner asserts that the previously submitted Sequence Listing and computer readable form do not comply with the requirements of 37 CFR §1.821- §1.825 in that a sequence of four amino acids appearing on page 22 was not included. This is remedied by the substitute Sequence Listing provided herewith and the computer readable form that accompanies this paper. A statement pursuant to 37 CFR §1.825(a) and (b) is also submitted.

In the Office Action, page 2/paragraph 2, the Examiner notes that the specification does not contain an Abstract. The specification has been amended in response to insert an Abstract of the Disclosure, and a separate page containing the Abstract is provided with this paper.

In the Office Action, page 3/paragraphs 3-4, claims 4 and 11-13 have been rejected under 35 U.S.C. §112, first paragraph, in that the specification is deemed not to enable the full scope of the Kunitz domain proteins as claimed. Reconsideration of this rejection is requested in view of the disclosure.

The Examiner asserts that,

> "Applicants have not described how to determine which plasma kallikrein inhibiting protein molecules hav[ing] substantial homology to the native molecule will have the same characteristics or function in the same manner as the protein itself. Nor is it disclosed whether these derivatives that have substantial homology may include mutations, insertions, or deletions at either the nucleic acid or amino acid level. Further, there is no indication of a level of activity which must be obtained in order to have a useful inhibitory protein variant or polypeptide fragment." (Office Action, paragraph 4)

To the contrary, claim 4 (and by incorporation the method claims 11-13 also) specifically defines the protein of the claim as a "kallikrein inhibiting protein" having an amino acid sequence "substantially homologous" to specifically recited reference sequences isolated according to Examples 1 and 2 (see pages 20-22). The quoted terms are specifically defined by Applicants at pages 5 and 6 of the specification, and the definitions include characteristic functions, structure, and level of activity, and describe permitted variations on the specified

sequences. Furthermore, examples of Kunitz domains in accordance with the invention, and examples of permissible modifications to the amino acid sequence are given throughout the specification: see, especially, page 6 (line 17) to page 7 (line10) and page 9 (line 26) to page 10 (line 16). Additionally, Applicants discuss at page 14 (line 31) to page 15 (line 23) three particular methods for testing a protein for kallikrein binding and inhibition, and provide specific illustrations of the preferred method in Examples 1 and 2. Accordingly, it is respectfully submitted that the hypothetical person skilled in the art would find sufficient guidance in the specification to practice the invention, and claims 4 and 11-13 are adequately enabled within the meaning of 35 U.S.C. §112, first paragraph.

In the Office action, page 4/paragraphs 5-6, claims 5, 8 and 11 have been rejected under 35 U.S.C. §112, first paragraph, in that the specification is deemed not to provide an enabling disclosure for methods of using the disclosed Kunitz domain proteins for prevention, as opposed to treatment, of kallikrein-mediated disorders. Reconsideration of this rejection is requested in view of the disclosure.

The Examiner asserts that,

> "Applicants have not described how to determine which kallikrein inhibitory protein molecules will completely prevent a condition such as excessive bleeding from causes such as coagulation defects or surgery. While it is taught that these conditions will be treatable, at least to some extent, by such a kallikrein inhibitory protein, there is no data that they will be completely prevented." (Office Action at paragraph 6)

At page 15 (lines 26-29) of the Applicants' disclosure, it is pointed out that "prevention" involves administration of a drug prior to the induction of disease, whereas "treatment" involves administration of drug after the appearance of disease. On page 16 (line 2) Applicants specifically teach that protection (which includes prevention) need not be absolute to be useful.

The kallikrein inhibitory proteins of the present invention will be effective against a diagnosed disease based on their ability to block the catalytic activity of a kallikrein (see page 5, lines 28-30); and that ability will be present whether the protein is administered prior to or after the appearance of the disease. The preamble of each of the rejected claims presumes "a disorder attributable to excessive kallikrein activity", and in such a medical context administration of a kallikrein inhibitor according to the invention prior to induction of the disease (i.e., "preventive" administration) can be expected to have a beneficial therapeutic effect, even if not absolute (which Applicants have taught is not required for the preventive administration to be useful).

For the foregoing reasons, in view of the definitions of the claim terms set forth in the application, no experimentation will be necessary on the part of a person skilled in this art to practice the methods of claims 5, 8 and 11 as they are presently claimed. Accordingly, withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

In the Office Action, page 6/paragraph 7, claims 4, 6-7, 9-10 and 12-13 have been rejected under 35 U.S.C. §112, second paragraph, for the reasons that:

- the use of the term "substantially homologous" is deemed to be unclear,
- inappropriate capitalization appears in one claim,
- sequence identification numbers are believed to be necessary to clarify claim 4,
- the process steps and source of the tested sample are deemed to be unclear in claims 6, 9 and 12, and
- antecedent basis for the term "analogue" and a clearer statement of the process steps are deemed to be necessary in claims 7, 10 and 13.

Reconsideration of the rejection in view of the amendments and the following remarks is requested.

With regard to "substantially homologous", this term is specifically defined at page 6 of the specification, and Table 2 sets forth nearly three dozen standard sequences to be used as reference points. Furthermore, when "substantially homologous" is considered together with other defined recitations of the claim (e.g., "kallikrein inhibiting protein"), the claim as a whole is sufficiently clear to meet the requirements of 35 U.S.C. §112, second paragraph.

With regard to "AND" appearing in claim 4, this has been amended to lower case letters.

With regard to addition of sequence identification numbers to the reference proteins of claim 4, this has been accomplished by the foregoing amendments.

With regard to the objections to claims 6, 9 and 12, these have been addressed by amendments made to the claims herein, and Applicants believe the amended claims are sufficiently clear to satisfy the requirements of 35 U.S.C. §112, second paragraph.

With regard to the recitation of "analogue" in claims 7, 10 and 13, without addressing or acceeding to the merits of the Examiner's objection, Applicants have eliminated this term from the claims, in order to advance this case toward allowance. The amendments should not be construed as an intention on Applicants' part to abandon any originally disclosed subject matter.

In view of the foregoing amendments, Applicants believe the rejections under 35 U.S.C. §112, second paragraph, have been avoided or overcome, and consequently withdrawal of the rejections is earnestly requested.

In the Office Action, claims 1-5, 8 and 11 have been provisionally rejected under the doctrine of obviousness-type double patenting in view of claims 1-4 of copending application Ser. No. 08/208,264, which is a parent application to the present application. Applicants' acknowledge the statement of this rejection by the Examiner and acknowledge the connection between the two cases. However, Applicants will address the issue of double patenting when amendment of the current claims is completed and allowable subject matter is determined to be present, at which point the provisional rejection may no longer apply.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants believe the claims are now in condition for allowance, and therefore reconsideration of the claims and withdrawal of the rejections are respectfully solicited.

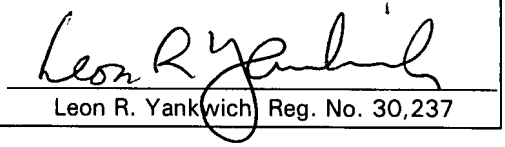
Respectfully submitted,

Leon R. Yankwich
Registration No. 30,237
Attorney for Applicants
YANKWICH & ASSOCIATES
130 Bishop Allen Drive
Cambridge, Massachusetts 02139
telephone: (617) 491-4343
telefax: (617) 491-8801

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as First Class Mail, postage prepaid, in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231 on the date indicated below.

Dec. 17, 1997
date



Leon R. Yankwich Reg. No. 30,237